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Title:	Substances and agents for positively influencing collagen
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The attached documents are a true and accurate copy of the original documents for this patent application.

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Tiedtke — Bühling — Kinne & PARTNERS (GbR)

Tiedtke – Bühling – Kinne, POB 20 19 18, D-80019 Munich

Patent Agents/ EPO Representatives *

Dipl.-Ing. Harro Tiedtke *
Dipl.-Chem. Gerhard Bühling *
Dipl.-Ing. Reinhard Kinne *
Dipl.-Ing. Hans-Bernd Peilmann *
Dipl.-Ing. Klaus Grams *
Dipl.-Biol. Dr. Annette Link
Dipl.-Ing. Aurel Volinhals *
Dipl.-Ing. Thomas J.A. Leson *
Dipl.-Ing. Hans-Ludwig Trösch *
Dipl.-Ing. Dr. Georgi Chivarov *
Dipl.-Ing. Matthias Grill *
Dipl.-Ing. Alexander Kühn *
Dipl.-Chem. Dr. Andreas Oser *
Dipl.-Ing. Rainer Böckelen *

Bavariaring 4, D-80336 Munich

13. August 13, 1999
DE 23764 / Case AS/EA

GENESISCOSMETICS RIGHTS & LICENSES COMPANY LTD.
9490 Vaduz, Liechtenstein

"Substances and agents for positively influencing collagen"

Telephone: 089 - 544690
Fax (G3): 089 - 532611
Fax (G4): 089 - 5329095

Deutsche Bank (Munich) Account No. 286 1060 (BRN 700 700 10)
Dresdner Bank (Munich) Account No. 3939 844 (BRN 700 800 00)
Postal Bank (Munich) Account No. 670 - 43 - 804 (BRN 700 100 80)
Dai-Ichi-Kangyo Bank (Munich) Account No. 51 042 (BRN 700 207 00)
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Description

The present invention relates to the use of substances and agents for positively influencing collagen, in particular not systemically but, rather, topically in collagen-containing parts of the body, such as tendons, fasciae, ligaments, cartilage, bone, dentin, and in particular topically on the skin. In the sense of the invention, "positively influencing" means essentially a stabilization, increase, and/or restoration of collagen or collagen fibers. Although not limited thereto, the invention is described mainly with respect to positively influencing the collagen in the skin (cutis), in which the collagen is a primary component of the dermis and epidermis. In addition to the treatment of collagen-associated problems in other parts of the body containing large amounts of collagen, the invention may be used in particular for the cosmetic treatment of unwanted conditions in the dermis, for example slackening of the epidermis or overstretching of the skin, such as the treatment of wrinkles, stretch marks, or tightening of the epidermis, primarily on the face and upper arm.

According to prevailing opinion, the skin is an estrogen-dependent organ, the collagen content of which decreases at menopause. The collagen of the skin is essentially of Type I. M.L. Barklink et al. (J. Appl. Physiol. 1993, 74(2), pp. 727-732) have found that bone mass and the collagen content of the skin decrease with increasing age. It has been found that a correlation exists between reduced collagen content of the skin and the decreased estrogen level in the blood which accompanies menopause with increasing age. D. Gruber et al. (Klin. Wochenschrift (Vienna) 1995, 107, pp. 622-625) have reported that the estrogen-dependent, postmenopausal decrease in collagen tissue may be evaluated using ultrasound, and have stated that successful treatment is possible by

optimizing the dosage in estrogen replacement therapy (hormone replacement therapy (HRT)). Other experts (see, for example, Therapie 1996, 51, pp. 67-70; and Dermatology 1996, 193, pp. 289-294) have attempted to combat aging of the skin, in particular that which occurs post-menopause, by use of HRT.

However, no evidence has been provided that estrogens are able to increase the collagen content of the skin. Thus, estradiol implants result in a marked reduction in the immature hydroxylysinorleucine "crosslinks" (Holland 1994). The percentage of collagen content and the proportion of mature "crosslinks" (histidinohydroxylysinorleucine) in the skin do not change.

Hormone replacement therapy (HRT) does not change either the quantity or the synthesis rate of collagen in the skin (Haapasaari 1997). In isolated cases it has been found that the relative proportion of Type III collagen increases following administration of estrogen (Savvas 1993, Schmidt 1996).

The object of the invention is to positively influence the collagen in affected parts of the body containing large amounts of collagen in order to assist in the stabilization, increase, and/or restoration of the collagen. A particular aim of the invention is to provide the possibility of cosmetically treating and positively influencing age-related adverse conditions of the skin such as wrinkles or lines.

The object is achieved by use of a substance or a composition containing this substance, wherein the substance, which is to be applied topically, inhibits the formation and/or the activity of estrogens, thereby stabilizing, increasing, and/or restoring the collagen in the bodily parts containing collagen.

Surprisingly, it has been found that the effects of the referenced substance or a composition containing this substance have a positive influence on the collagen, in particular the content of collagen fibers, in the skin, causing the skin to become firmer. Biopsies have confirmed that the proportion of collagen fibers has increased. It is considered that, in fundamental contrast to the natural, systemic influence via the estrogen level in the blood, and compared to known estrogen replacement therapy (HRT), a beneficial effect on collagen may be achieved at specific target sites when the localized extragonadal estrogen formation and/or the localized activity of estrogens is inhibited by use of the particular substance or composition containing this substance, administered according to the invention.

In the treatment of collagen deficiency conditions of the epidermis, for example slackening of the epidermis, wrinkle formation, and stretch marks, it has been found that the positive influence on the collagen is exerted locally in the cutis, i.e., in the epidermis and dermis.

The substances and their capability for treatment of subcutaneous fatty tissue problems such as cellulite, and use thereof for tightening and/or reducing the size of bodily parts containing fat cells are known in part from WO-A 97/36570 and WO-A 99/17712. However, the conditions in the subcutaneous fatty tissue described in the cited documents occur in the subcutis, whereas the present invention targets the elements of the body in particular containing collagen, namely, the cutis (epidermis and dermis), as well as other parts containing large amounts of collagen, such as tendons, fasciae, ligaments, cartilage, bone, and the like. The cited documents in particular contain no references to the unexpectedly discovered relationship between inhibition of formation on the one hand and, on the other hand, the effect of localized estrogen and positive, direct influence on

the localized collagen in the cutis, which is anatomically and functionally different from the subcutis.

Consequently, according to the present invention, functional penetration of the skin into the subcutis is not necessary to realize the described effects in the cutis itself. The positive influencing of the collagen according to the invention occurs directly in the epidermis and in the dermis of the cutis on account of the relative deficiency of estrogen. This is because the cutis of the skin is able to form estrogens from androgens (Bulun 1998), since fibroblasts (Macdiarmid 1994, Toda 1994, Staib 1994, Jakob 1995, Isurugi 1996) as well as keratinocytes (Hughes 1997) contain the aromatase enzyme. Furthermore, the epidermis and dermis are estrogen-dependent layers of the skin, and therefore must have estrogen receptors (Hughes 1997 (keratinocytes), Dieudonne 1998 (fibroblasts)). Since the aromatase activity in the skin (particularly in females) is constitutively pronounced and estrogens reduce the content of collagen fibers, the skin of females constitutively does not contain as many collagen fibers as the skin of males, which is also much thicker. Lowering the localized estrogen concentration in the skin of females results in an increase in collagen fibers. Because the estrogen concentration in the skin of females is largely the result of localized activity of aromatase, inhibition of the aromatase activity in the keratinocytes and dermal fibroblasts lowers the localized estrogen concentration. Thus, inhibition of the skin aromatase results in an increase in collagen fibers, in particular those of Type I, thereby increasing the thickness and tightness of the skin. These phenomena are observed in female test subjects studied within the scope of the invention after administration for approximately four weeks, and have been experimentally verified.

The term "estrogens" is understood to mean all natural female sexual hormones having an estrogenic effect, such as estradiol, estrone, and estrol.

According to the present invention, two classes of substances in particular are considered as substances which form estrogen and/or inhibit the activity of estrogen, and are described below in greater detail.

The first class is the antiestrogens, i.e., substances which block estrogen receptors and which as antagonists therefore inhibit the activity of estrogen.

The second class is substances which are able to locally inhibit extragonadal estrogen formation. Considered for this purpose are primarily steroidal and nonsteroidal inhibitors of (cytochrome P450) aromatase. This aromatase represents the key enzyme which catalyzes the chemical conversion of the precursor molecules (such as dehydroepiandrosterone (DHEA) and androstenedione), which originate in the adrenal glands and are transported in the blood, into estrogens. The inhibition of this enzyme results in localized in situ inhibition of estrogen formation. The aromatase inhibitors are preferred for use in the application according to the invention on account of their particularly advantageous activity mechanism.

Examples of aromatase inhibitors include the substances 4-hydroxyandrost-4-ene-3,17-dione (Formestan™), 6-methyleneandrostra-1,4-diene-3,17-dione (Exemestan™), 10-(2-propynyl)estr-4-ene-3,17-dione (MDL 18962), with 7α-substituted androstendione derivatives as examples of steroidal aromatase inhibitors, and imidazole and triazole derivatives as examples of nonsteroidal aromatase inhibitors, such as 6-[(4-chlorophenyl)(1H-1,2,4-triazol-l-yl)methyl]-1-methyl-1H-benzotriazole (Vorazol™), 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-

phenylene]-bis(2-methylproprionitrile) (Arimidex™), 4-[1-(cyanophenyl)-1-(1,2,4-triazolyl)methyl]benzonitrile (Letrozol™), {4-(5,6,7,8-tetrahydroimidazo-[1,5a]pyridin-5-yl)benzonitrile monohydrochloride (Fadrozol™), and pyridoglutethimide (Rogletimid™).

For descriptions of these substances and availability information, see, for example, "Red List," Editio Cantor, Aulendorf (DE), 1985.

Such aromatase inhibitors are known as such as systemically administered active substances for medical-therapeutic treatment of breast cancer. In this regard, reference is made to the overview articles by A.M.H. Brodi in J. Steroid Biochem. Molec. Biol., Vol. 49, No. 4-6, pp. 281-287 (1994), and P. E. Goss and K.M.E.H. Gwyn in Journal of Clinical Oncology, Vol. 12, No. 11, pp. 2460-2470 (1994). For the determination of aromatase inhibition and subsequent estrogen reduction, reference is made to the further literature citations listed in the referenced overview articles; see, for example, A.M.H. Brodi et al. in J. Steroid Biochem. Molec. Biol., Vol. 7, pp. 787-793 (1976), and D.A. Marsh et al. in J. Med. Chem., Vol. 28, pp. 788-795 (1985).

Specific azol derivatives and their aromatase-inhibiting and antimycotic activity are further described in EP-A-0 575 210.

It has been shown that glycine soja (INCI name according to the Linné system) contains substances having aromatase-inhibiting properties, and that these aromatase inhibitors originating from glycine soja may be used within the scope of the present invention. These aromatase inhibitors originating from glycine soja may be easily obtained by providing glycine soja (soybean oil or soybean extract, or soy sterol) and subsequent isolation of the component having an aromatase-

inhibiting effect by use of customary separation methods such as liquid chromatography, in particular HPLC.

It has also been found that the aromatase inhibitor effect of the glycine soja may be enhanced by subjecting the glycine soja to oxidation.

This oxidized form originating from glycine soja may be easily prepared by oxidation of the glycine soja (soybean oil or soybean extract, or soy sterol) and subsequent isolation of the component having an aromatase-inhibiting effect by use of customary separation methods such as liquid chromatography, in particular HPLC.

The oxidation may [be carried out] using an enzymatic approach, for example according to the methods described by Y. Fujimoto et al. in J. Am. Chem. Soc., Vol. 104, pp. 4718-4720 (1982), or using a chemical approach, for example according to the methods described by P. Welzel in Tetrahedron, Vol. 41, No. 20, pp. 4509-4517 (1985).

Mentioned in particular as examples of substances of the antiestrogen class are the nonsteroidal estrogen antagonists tamoxifen (Z-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylamine) and aminoglutethimide (3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione) and the analogs and derivatives thereof, for example 3-hydroxytamoxifen, 4-hydroxytamoxifen, and the 7-α-alkylsulfinyl tamoxifen analogs (ICI 182,780).

For descriptions of these substances and availability information, see, for example, "Red List," Editio Cantor, Aulendorf (DE), 1985.

These antiestrogens as well have been described hitherto primarily in conjunction with the systemic therapeutic treatment of breast cancer.

To enable the activity mechanisms to be mutually complemented and favorably influenced, according to one preferred embodiment a composition containing a combination of one or more aromatase inhibitors and one or more antiestrogens is used for topical administration. The quantity ratio used in the combination is not critical, and may be adapted to the particular requirements. Thus, for example, in each case one substance type or the other may predominate, depending on the preferred activity pathway. The weight-based quantity ratio of aromatase inhibitor to antiestrogen is in a range, for example, of 90/10 to 10/90, in particular 60/40 to 40/60.

For positively influencing the collagen in the cutis of the skin, a suitable formulation of the substance to be used, for example an ointment, cream, gel, emulsion (lotion), powder, oil, etc., may be selected for topical administration of the substance or composition. For this purpose, the composition contains additives customary for the corresponding formulation as an ointment, cream, gel, emulsion, powder, oil, etc. Customary, commercially available skin care agents, in addition to those described, are best suited in the particular formulations for use in the present invention. Examples of common additives used for such formulations include plant oils such as almond oil, olive oil, peach kernel oil, peanut oil, castor oil, and the like, plant extracts, etheric oils, vitamin oils, fats and fatlike substances, lipoids, phosphatides, hydrocarbons, and paraffins, Vaseline, lanolin, waxes, and the like, detergents, further active ingredients for the skin such as lecithin, lanolin alcohols, carotene, and the like, skin nutrients, fragrances, cosmetic substances, alcohols, glycerol, glycols, urea, talc, preservatives,

sunscreens, dyes such as titanium white and zinc white, antioxidants, etc. Water is usually used as base, generally resulting in an O/W or W/O emulsion when emulsifiers such as fatty alcohol sulfates, alkali soaps, lecithins, triethanolamine, and the like are added.

The quantity of active substance in such formulations for inhibition of the estrogen formation or activity is not critical, and may be adapted to the particular application. An active substance content of, for example, 0.0001 to 10 percent by weight (%-wt), preferably 0.001 to 5%-wt, and in particular 0.3 to 2%-wt, in the overall composition is suitable. The further additives which are optionally present may be used in quantities customary for the particular formulations.

Based on the surprising discovery of the possibility for stabilizing, increasing, and/or restoring collagen in the cutis of the skin by means of the specific substances, the invention may be used not only for this application, but also for other collagen-containing parts of the body as localized target areas of administration, such as cartilage, tendons, ligaments, fasciae, dentin, bone, and the like. Thus, the substance or the composition containing this substance may be used to support in surgical procedures involving such bodily parts containing large amounts of collagen. Use for cosmetic purposes, for example in cosmetic surgery, is preferred. However, the substance or composition to be used according to the invention is also suited as an alternative to surgical measures, for example to develop or build up cartilage mass, or to strengthen tendons and ligaments. Another advantageous area of application, therefore, is sports medicine, where it may be used to counteract wear or even injuries to tendons, ligaments, muscle,

and cartilage caused by athletic stress. Injection of physiologically acceptable solutions or suspensions containing one or more of the described substances in or at the target site, for example, is suitable for such administration in the body. The types of carrier fluid and other components depend on the particular site of administration, and are known to one skilled in the art.

The invention is explained below with reference to several examples.

Example 1) Eye wrinkle ointment (25 mL)

Cetylstearyl alcohol	3.5 mL
Sodium lauryl sulfate	0.75 mL
Liquid paraffin	5.0 mL
White Vaseline	15.5 mL
Oxidized glycine soja with aromatase-inhibiting activity	0.15 mL

1.1. A 60-year-old male with very pronounced development of lines in the area around the eyes, in particular the lower and upper eyelids:
Tightening in the area of the eyelids, and almost complete disappearance of lines after 1x daily treatment for 10 weeks.

1.2. A 50-year-old female with pronounced development of lines around the eyes; status 5 years following a facelift.
Marked tightening of the epidermis in the area of line development around the eyes after 2x daily administration with the composition from Example 1) for 8 weeks; after 16 weeks the lines had disappeared to the extent that the subject reported

that her appearance is now better than after the facelift.

Example 2) Face cream (50 mL)

Propylene glycol	12.5 mL
Isopropyl myristate	3.0 mL
Sorbitan monostearate	0.5 mL
Polysorbate 80	1.0 mL
Stearyl alcohol	1.0 mL
Cetylstearyl alcohol	3.0 mL
Glycerol monostearate	0.5 mL
Oxidized glycine soja with aromatase-inhibiting activity	0.25 mL
Distilled water	To 50.0 mL

A 47-year-old female with heavy wrinkle development in the lower facial area, primarily in the area of the cheeks and chin: Tightening of the wrinkles was perceptible and visible after 2x daily treatment with the composition from Example 2) for 6 weeks; after 12 weeks only small lines were visible.

Example 3) Upper arm cream lotion (100 mL)

Span 80	1.0 mL
Span 60	5.0 mL
Tween 60	9.0 mL
Propylene glycol	15.0 mL
Palmitic acid	9.0 mL
Oxidized glycine soja with aromatase-inhibiting activity	0.4 mL
Distilled water	To 100.0 mL

A 43-year-old female with epidermal wrinkles on the upper arms; 2x daily treatment with the cream lotion; marked tightening was perceptible after 4 weeks; after 8 weeks marked tightening was perceptible and visible; after 12 weeks wrinkling was greatly reduced; after 16 weeks wrinkling was essentially undetectable. (Micrographs of pre- and post-treatment biopsies showed an increase in collagenic fibers in the skin; Figure 1 before treatment, and Figure 2 after treatment for 16 weeks)

Example 4) Gel for stretch marks (100 mL)

Microcrystalline cellulase [sic]	4.0 mL
Polyethylene glycol 400	5.0 mL
Cetyl alcohol	10.0 mL
Oxidized glycine soja with aromatase-inhibiting activity	0.4 mL
Distilled water	To 100.0 mL

4.1. A 27-year-old female, two births, with pronounced pregnancy stretch marks in the area of the abdomen; 2x daily administration of the gel cream; Findings: after 6 weeks mild tightening was perceptible; after 12 weeks the stretch marks were greatly reduced; after 18 weeks the stretch marks were no longer visible.

4.2. A 25-year-old female after multiple diets; stretch marks on the thighs and buttocks. Findings: after 5 weeks, reduction in stretch marks primarily on the thighs; after 10 weeks the stretch marks

on the buttocks and thighs had (almost) disappeared; after 15 weeks all stretch marks were practically invisible: Figure 3 before treatment, Figure 4 after treatment for 10 weeks.

Example 5) Injection form for intrafocal administration (1 mL)

15 mg 4-hydroxyandrostendione (formestan)
Adjuvants: Benzyl alcohol, carmellose-Nd, polysorbate, sodium chloride, water

A 30-year-old female tennis player (Federal League) with pronounced signs of overstretching on both knee joints (ligaments and tendons), severe pain; playing tennis was possible only while wearing bandages on both sides and under medication with nonsteroidal anti-inflammatory drugs (NSAID). Injection of the composition from Example 5) into the knee joints at 2-week intervals over a period of 10 weeks: greatly reduced use of NSAID after the third injection (at 4 weeks); after 10 weeks the subject was able to play with essentially no pain (without NSAID), and perceived a stabilization of the knee joints.

Tiedtke — Bühling — Kinne & PARTNERS (GbR)

Tiedtke – Bühling – Kinne, POB 20 19 18, D-80019 Munich

Patent Agents/ EPO Representatives *
Dipl.-Ing. Harro Tiedtke *
Dipl.-Chem. Gerhard Bühling *
Dipl.-Ing. Reinhard Kinne *
Dipl.-Ing. Hans-Bernd Pellmann *
Dipl.-Ing. Klaus Grams *
Dipl.-Biol. Dr. Annette Link
Dipl.-Ing. Aurel Vollnhals *
Dipl.-Ing. Thomas J.A. Leson *
Dipl.-Ing. Hans-Ludwig Trösch *
Dipl.-Ing. Dr. Georgi Chivarov *
Dipl.-Ing. Matthias Grill *
Dipl.-Ing. Alexander Kühn *
Dipl.-Chem. Dr. Andreas Oser *
Dipl.-Ing. Rainer Böckelen *
Bavariaring 4, D-80336 Munich

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CLAIMS

1. Use of substances which inhibit the formation and/or activity of estrogens, or use of a composition containing one of these substances, for topical administration for stabilizing, increasing, and/or restoring collagen.

2. Use according to Claim 1, **characterized in that** the substance is selected from the group comprising aromatase inhibitors and antiestrogens.

3. Use according to Claim 1, **characterized in that** the substance is an aromatase inhibitor.

4. Use according to Claim 1, **characterized in that** the substance originates from glycine soja.

5. Use according to Claim 1, **characterized in that** the substance composed of glycine soja is subjected to oxidation.

Telephone: 089 - 544690
Fax (G3): 089 - 532611
Fax (G4): 089 - 5329095

Deutsche Bank (Munich) Account No. 286 1060 (BRN 700 700 10)
Dresdner Bank (Munich) Account No. 3939 844 (BRN 700 800 00)
Postal Bank (Munich) Account No. 670 - 43 - 804 (BRN 700 100 80)
Dai-Ichi-Kangyo Bank (Munich) Account No. 51 042 (BRN 700 207 00)
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6. Use according to one of the preceding claims, **characterized in that** the substance is contained in a composition in a quantity of 0.001 to 5% by weight relative to the total quantity of the composition.

7. Use according to one of the preceding claims, **characterized in that** the composition includes an aromatase inhibitor and an antiestrogen.

8. Use according to one of the preceding claims, **characterized in that** the topical administration is used for cosmetic purposes.

9. Use according to one of the preceding claims, **characterized in that** the purpose of use is to stabilize, increase, and/or restore collagen in the skin.

10. Use according to Claim 9, **characterized in that** the substance is contained in a composition which is formulated as an ointment, cream, gel, oil, or emulsion (lotion).

11. Use according to one of Claims 8 through 10, **characterized in that** wrinkles and/or stretch marks on the skin and slackening of the epidermis are cosmetically treated.

12. Use according to one of Claims 1 through 8, **characterized in that** the purpose of use is to stabilize, increase, and/or restore collagen in tendons, fasciae, ligaments, cartilage, bone, or dentin.

13. Use of a substance and/or substances which inhibit(s) the formation and/or activity of estrogens, or use of a composition containing this substance or substances, for preparing an agent for stabilizing, increasing, and/or restoring collagen.

14. Use according to Claim 13, characterized in that a substance or a composition is used as defined in one of Claims 2 through 7.

Tiedtke — Bühling — Kinne & PARTNERS (GbR)

Tiedtke – Bühling – Kinne, POB 20 19 18, D-80019 Munich

Patent Agents/ EPO Representatives *
Dipl.-Ing. Harro Tiedtke *
Dipl.-Chem. Gerhard Bühling *
Dipl.-Ing. Reinhard Kinne *
Dipl.-Ing. Hans-Bernd Pellmann *
Dipl.-Ing. Klaus Grams *
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Dipl.-Ing. Aurel Volinhals *
Dipl.-Ing. Thomas J.A. Leson *
Dipl.-Ing. Hans-Ludwig Trösch *
Dipl.-Ing. Dr. Georgi Chivarov *
Dipl.-Ing. Matthias Grill *
Dipl.-Ing. Alexander Kühn *
Dipl.-Chem. Dr. Andreas Oser *
Dipl.-Ing. Rainer Böckelen *
Bavariaring 4, D-80336 Munich

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ABSTRACT

The invention describes the use of a substance and/or substances, or use of a composition containing this substance and/or substances, wherein this substance and/or substances inhibit(s) the formation and/or activity of estrogens, for topical administration for stabilizing, increasing, and/or restoring collagen.

Aromatase inhibitors and/or antiestrogens in particular are used as suitable substances.

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Fax (G3): 089 - 532611
Fax (G4): 089 - 5329095

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Key to Figures

Abb. = Figure